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(54) Title: FREE RADICAL-CATALYZED SYNTHESIS OF BENZOPROSTACYCLINS

(57) Abstract

A method is provided for preparing benzoprostacyclins by the free-radical-catalyzed tandem alkene insertion into a 1,4-bi-soxy-substituted cyclopent-2-ene intermediate.

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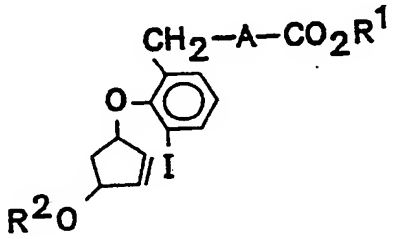
WHAT IS CLAIMED IS:

1. A method for preparing benzoprostacyclins comprising reacting a compound of the general formula (III):

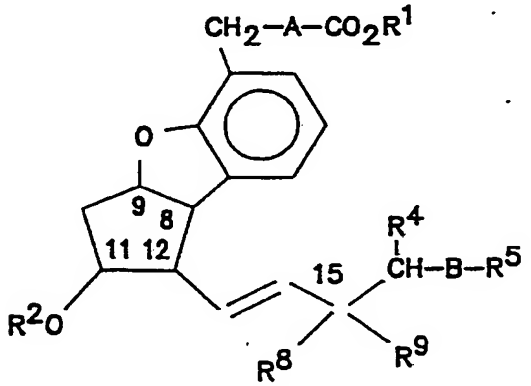


(III)

wherein R^1 is a pharmaceutically-acceptable cation, H or (C_1-C_{12})alkyl; A is $-CH_2-$, $-O-CH_2-$, $-CH_2-CH_2-$ or $-CH=CH-$; and R^2 is H, (C_1-C_{12})alkyl, (C_1-C_{10})acyl or (C_7-C_{13})aroyl with a compound of a general formula (IV):

$$R^7-CH=CH-C(O)-CH(R^4)-B-R^5 \quad (IV)$$

wherein R^5 is (C_1-C_5)alkyl; B is $-(CH_2)_n-Z$ wherein n is 0-4 and Z is $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$; R^4 is H, F, CH_3 or CH_2CH_3; and R^7 is $((C_1-C_4)alkyl)_3Sn$ or $(phenyl)_3Sn$ wherein the reaction is carried out in the presence of a catalytic amount of a free radical initiator to yield a compound of the formula (II):



(II)

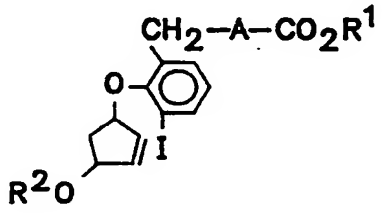
wherein R^8 and R^9 taken together are keto, and R^1, A, R^2, R^4, B and R^5 are as defined above.

2. The method of claim 1, further comprising reducing the C_{15}-keto group of compound II with a reducing agent to yield a compound of formula II wherein R^8 is H and R^9 is OH.

3. The method of claim 1 wherein, in compound III, R^1 is (C_1-C_{12})alkyl and R^2 is H.

4. The method of claim 1 wherein the mole ratio of III:IV is about 1:1.25-20.

5. A method for preparing benzoprostacyclins comprising reacting a compound of the general formula (III):

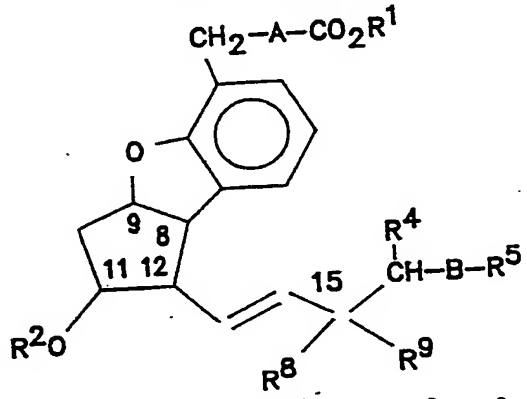


wherein R^1 is a pharmaceutically acceptable cation, H or (C_1-C_{12})alkyl; A is $-CH_2-$, $-O-CH_2-$, $-CH_2-CH_2-$ or $-CH=CH-$; and R^2 is H, (C_1-C_{12})alkyl, (C_1-C_{10})acyl or (C_7-C_{13})aroyl with a compound of the general formula (V):

$$R^7-CH=CH-C(R^8)(OR^3)-CH(R^4)-B-R^5 \qquad (V)$$

wherein R^5 is (C_1-C_5)alkyl, B is $-(CH_2)_n-Z$ wherein n is 0-4 and Z is $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$; R^4 is H, F, CH_3 or CH_2CH_3; R^7 is $((C_1-C_4)\text{alkyl})_3Sn$ or $(\text{phenyl})_3-Sn$, R^8 is (C_1-C_{12})alkyl or H; and R^3 is H, (C_1-C_{12})alkyl, (C_1-C_{10})acyl or (C_7-C_{13})aroyl; wherein the reaction is carried out in the

presence of a catalytic amount of a free radical initiator to yield a compound of the formula II:



(II)

wherein R^9 is OR^3, and R^1, A, R^2, R^3, R^4, B, R^5 and R^8 are as defined above.

6. The method of claims 1 or 5 wherein R^7 is $(n\text{-butyl})_3Sn$.

7. The method of claim 5 wherein R^3 is H in compounds II and V.

8. The method of claims 1 or 5 wherein compound II comprises $(S)C_{15}$-OH.

9. The method of claim 8 wherein the C_{11}-OR^2 bond is in the alpha-configuration.

10. The method of claims 1 or 5 further comprising saponifying the CO_2R^1 moiety of compound II and neutralizing the reaction mixture to yield CO_2H.

11. The method of claim 10 further comprising forming a pharmaceutically acceptable alkali metal salt, ammonium, or amine salt of the moiety CO_2H.

12. The method of claims 1 or 5 wherein the free radical initiator is AIBN.

13. The method of claims 1 or 5 wherein the reaction is carried out in solution in an organic solvent.

14. The method of claim 13 wherein the reaction is carried out at about 50-150°C.

15. The method of claim 14 wherein the reaction is carried out for about 5-48 hours.

16. The method of claims 1 or 5 wherein A is $-CH_2-$ or $-CH_2-CH_2-$ and B is $CH_2-CH_2-CH_2$.

17. The method of claim 16 wherein R^4 is H and R^5 is CH_3.